Evaluation of Recurrence in 36 Subacute Thyroiditis Patients Managed with Prednisolone

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Abstract

Objective The incidence of subacute thyroiditis (SAT) is low and there are a few reports of recurrence of subacute thyroiditis. Current treatment protocols for SAT are not uniform. Prednisolone (PSL) is chosen more often for treatment than nonsteroidal anti-inflammatory drugs. This study was undertaken to confirm the recurrence rate of SAT managed by PSL, and to compare the initial laboratory data between the recurrent and the non-recurrent groups.

Methods After diagnosis, all patients were treated with PSL (starting at 30 mg or 25 mg per day, tapered by 5 mg per week) for 5 or 6 weeks. We evaluated data and symptoms at the first visit and during the therapy.

Patients Thirty-six patients who received only PSL for SAT at our hospital between January 1997 and December 1998 were referred. These patients asked to visit every 2 weeks for the monitoring of symptoms and laboratory data.

Results SAT symptoms recurred in eight patients (22%), most upon cessation of PSL. There was no difference in initial serum sialic acid, erythrocyte sedimentation rate, C-reactive protein, Thyroglobulin (Tg) and serum sialic acid (SA) increase in the acute phase of this disease. Another diagnostic characteristic for SAT is low uptake of iodine-131 on thyroid scan. Salicylates and nonsteroidal anti-inflammatory drugs are administered when symptoms are mild and the degree of inflammatory factors slight.

Generally, PSL is the preferred drug for the treatment of SAT primarily due to the quick relief of symptoms (1). There is little data available on the administration of PSL and various treatment protocols have been reported (2–5). Late (several years after recovery) recurrence of SAT is very rare (6–8). On the other hand, recurrence within one year of treatment is common. In this study, we reviewed our patients with SAT treated with PSL, and focused on the early recurrence of SAT. Here, we report a comparison of initial laboratory data between the recurrent and the non-recurrent groups and discuss the effects of our treatment protocol.

Materials and Methods

Patients

Thirty-six SAT patients (32 women and 4 men), aged 31–71 years who were diagnosed with SAT at the Noguchi Thyroid Clinic and Hospital Foundation during January 1997 to December 1998 were used for this study. Diagnosis of SAT was made as follows: 1) Typical clinical symptoms such as tenderness, fever, palpitation, body weight loss, general malaise, etc. 2) Elevation of the ESR, CRP, and SA. 3) Decreased uptake of radioactive iodine. 4) Absence of thyroid microsomal antibody (MCHA) and thyroglobulin antibody (TGHA). 5) Pseudocystic sign in ultrasonographic findings. Patients having other thyroid diseases or already taking PSL were excluded. No patients had received interferon therapy for chronic hepatitis.

After diagnosis, PSL was administered at 30 mg or 25 mg daily, and tapered by 5 mg per week, for 5 or 6 weeks; Ten patients were started from 30 mg per day for over 2 weeks and...
reduced by 5 mg per week. Sixteen patients were started from 30 mg per day for 1 week and reduced by 5 mg per week. Other 10 patients were started from 25 mg. During the therapy, we measured serum free thyroxine (FT4), free triiodothyronine (FT3), ESR, SA, white blood cell count (WBC), CRP, Tg, MCHA, and TGHA as frequently as possible. Cessation of the therapy was decided when it was at 5 mg daily, and there was no elevation of inflammatory agents, and the clinical symptoms had disappeared. Recurrence was defined as the presence of symptoms such as tenderness, painful goiter and elevation of inflammatory factors. Upon recurrence, PSL treatment was re-started at the initial dose or less.

**Laboratory evaluation**

FT4, FT3 and TSH were measured by chemiluminescent immunoassay using assay kits (Chiba Cornings Diagnostics Corp, Medfields, MA, USA). The normal ranges for free T4, free T3 and TSH are 9–21.9 nmol/l, 3.4–6.3 pmol/l, and 0.30–3.50 mU/l, respectively. SA levels were determined by enzymatic measurement with a commercially available kit (Sialic Acid-HA, 7150, Wako Pure Chemicals Industries, Ltd., Osaka). The normal range of SA is 42–75 mg/dl. CRP was measured with a commercially available kit (Auto TIA CRP S “Nissui”, Nissui Pharmaceutical Co., Ltd. Tokyo). Tg was measured by enzyme-immunoassay as we previously reported (9). MCHA and TGHA titers were measured by hemagglutination methods. The normal ranges are less than 15 mm/h (female), 10 mm/h (male) for ESR, less than 0.5 mg/dl for CRP, less than 83.4 pmol/l for Tg, and less than 1:20 titer for MCHA and TGHA.

**Statistical analysis**

Each value was expressed as the mean ± standard deviation. Student’s t-test and Chi square test were used for statistical analysis. Statistical analyses were performed using SAS-JMP3.2 software for Macintosh (SAS Institute Inc.).

**Results**

Most patients had thyrotoxicosis at the time of the first visit and became euthyroid by the second week. Thyrotoxic states included increased SA levels, CRP and classic symptoms. Of 36 patients, eight recurred (22%). Of ten patients started from 30 mg per day for over 2 weeks and reduced by 5 mg per week, two recurred (20%). Of sixteen patients started from 30 mg per day for 1 week and reduced by 5 mg per week, four recurred (25%). Of 10 patients started from 25 mg, two recurred (20%). They had the classic symptoms and elevated SA levels or other inflammatory factors. In all 36 patients, SA levels and symptoms were reduced by the next visit (after 2 weeks) to our hospital. Table 1 shows the clinical and biochemical data of eight recurrent patients. One patient recurred while receiving 10 mg per day of PSL, 4 patients recurred just at the cessation of PSL, and 3 patients shortly after the end of treatment. Of 8 recurrent patients, two patients recurred twice and one recurred 3 times. All recurrent patients received at total dosage of 1,000 mg PSL, nevertheless none suffered side effects such as diabetes mellitus, gastric ulcers, infections, or osteoporosis.

Case 5 recurred 3 times (Fig. 1). The first recurrence was 5 days after cessation of the therapy. Symptoms included tenderness, SA was elevated to 64.0 mg/dl, CRP was 0.84 mg/dl, FT4 was 18.0 nmol/l, and FT3 was 5.99 pmol/l. Treatment was readministered starting with 30 mg per day of PSL and was reduced 5 mg per week. The second recurrence occurred a month after cessation of the therapy. SA was elevated to 88.5 mg/dl, CRP was 8.05 mg/dl, FT4 was 47.6 nmol/l, and FT3 was 12.7 pmol/l. The third recurrence was similar to the prior episode; SA was elevated to 74.1 mg/dl, CRP was 2.46 mg/dl, FT4 was 30.9 nmol/l, and FT3 was 8.9 pmol/l. PSL was restarted. After cessation of the last therapy, symptoms and the elevation of SA were not seen.

There was no difference in the laboratory data before starting the therapy between recurrent and non-recurrent groups as measured by ESR, WBC, CRP, SA, Tg, FT3 and FT4 (Table 2).

**Table 1. The List of 8 Recurrent Patients, Sex, Age, 1st Recurrent Point, Sialic Acid and CRP and FT4, FT3 at 1st Recurrent Time, Recurrent Times, Total PSL Dose, Total Period for Therapy**

<table>
<thead>
<tr>
<th>Case</th>
<th>Sex</th>
<th>Age</th>
<th>1st recurrent point</th>
<th>Sialic acid (mg/dl)</th>
<th>CRP (mg/dl)</th>
<th>FT4 (nmol/l)</th>
<th>FT3 (pmol/l)</th>
<th>Recurrent times</th>
<th>Total PSL (mg)</th>
<th>Total period (month)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>49</td>
<td>At10 mg/day</td>
<td>89.3</td>
<td>0.65</td>
<td>23.17</td>
<td>7.99</td>
<td>1</td>
<td>1,225</td>
<td>2.5</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>71</td>
<td>just cessation</td>
<td>85.0</td>
<td>2.79</td>
<td>NT</td>
<td>NT</td>
<td>1</td>
<td>1,055</td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>47</td>
<td>just cessation</td>
<td>130.4</td>
<td>5.31</td>
<td>43.76</td>
<td>11.06</td>
<td>1</td>
<td>2,380</td>
<td>4</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>51</td>
<td>just cessation</td>
<td>77.8</td>
<td>0.00</td>
<td>NT</td>
<td>NT</td>
<td>2</td>
<td>1,715</td>
<td>7</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>41</td>
<td>just cessation</td>
<td>64.0</td>
<td>0.84</td>
<td>18.02</td>
<td>5.99</td>
<td>3</td>
<td>3,780</td>
<td>8</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>49</td>
<td>After 4 week</td>
<td>95.1</td>
<td>4.16</td>
<td>32.18</td>
<td>9.06</td>
<td>1</td>
<td>1,085</td>
<td>4</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>52</td>
<td>After 9 week</td>
<td>NT</td>
<td>2.46</td>
<td>NT</td>
<td>NT</td>
<td>2</td>
<td>1,245</td>
<td>4.5</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>57</td>
<td>After 18 week</td>
<td>88.4</td>
<td>1.02</td>
<td>15.44</td>
<td>5.38</td>
<td>1</td>
<td>1,015</td>
<td>8</td>
</tr>
</tbody>
</table>

NT: not tested.
Discussion

In this study, we examined the recurrence of SAT among 36 patients treated with PSL. There are several markers for monitoring SAT. Tg levels have been used as a marker in the early phase of SAT (2, 5, 7, 9). It is also reported that interleukin-6 (IL-6) concentrations increase in the thyrotoxic phase and normalize after remission (10). Yamada et al reported dissociation between IL-6 and other inflammation parameters (ESR, Tg, CRP) during treatment with PSL in SAT (11). IL-6 detection is not yet available as a commercial kit; therefore we were unable to include it in our studies. We focused mainly on serum sialic acid levels in SAT as we previously reported (3). SA levels were gradually reduced during the therapy and normalized by the time glucocorticoid therapy had been discontinued. Tg and ESR levels, however, remained above normal even at the time of cessation of the therapy. CRP soon returned to negative, within one or two weeks after initiation of the therapy.

In the treatment of SAT, there is no definitive treatment protocol. Yamada et al administered PSL 30 mg per day which was tapered gradually (30, 20, 10, 5 mg per day) at intervals of...
Recurrence in SAT Managed with PSL

7–10 days (11). Bennedbaek and Hegedus gave PSL at 37.5 mg per day for 2 weeks and reduced it by 12.5 mg every 2 weeks (12). Vagenakis et al begun PSL mainly at 30 mg per day but reduced it irregularly (4). Madeddu et al treated with betamethasone phosphate starting at 3 mg per day for 30 days and then tapered and discontinued in 80 days (2).

Generally PSL is used because of the quick relief of symptoms, most within 24 hours. In this study, symptoms such as tenderness and painful goiter disappeared within 1 or 2 days. The effect of PSL for SAT is to suppress the inflammation response. It is said that PSL treatment should be continued until the I-131 uptake rate returns to normal (4). If I-131 uptake rates do not return to normal, PSL should not be discontinued. We could not measure I-131 uptake rate at every visit to our hospital because the uptake rate counts require 24 hours and iodine restriction; therefore the I-131 uptake rate was used only for confirmation of recovery. It is also reported that PSL should not be stopped before the serum Tg concentration returns to normal (5). But TSH is one factor of Tg elevation. The elevation of Tg is concomitant with high TSH, too. We should give careful consideration to this elevation due to TSH.

The major problem with PSL administration is the high incidence of recurrence following withdrawal of the medication (4). Kitchener and Chapman reported 105 cases (13). In their 88 painful thyroiditis, recurrence occurred in only two patients. Bennedbaek and Hegedus showed 8 out of 23 patients recurred (35%), in their report (12). But generally, the recurrence rate for SAT is about 10–20% (1, 14), which is compatible with the present study. In this study, in all recurrent patients, the total dosage of PSL was over 1,000 mg, but no side effects of PSL, such as moon face, gastric ulcer, diabetes mellitus, infections, or osteoporosis were seen. SAT patients treated with corticosteroids should be monitored every 2 weeks for the advent of side effects.

Our present and previous reports show that there is no significant difference in laboratory data at first visit between recurrent and non-recurrent groups (3). This suggests there is no predictable laboratory data for recurrence. Two patients of ten who were initially administered PSL 30 mg daily over two weeks recurred. So, initial suppression of the thyroid inflammation is thought to be enough with one week of PSL at 30 mg daily. It has been previously reported that recurrence occurs when PSL is reduced to the 10 to 20 mg per day range or immediately after discontinuation of the therapy (14). In the present study, one patient recurred during the reduced PSL dosage, the other seven recurred immediately upon cessation of PSL or shortly thereafter. We speculate that the period of PSL at 10 mg daily may be a break point for recurrence, and there may be a need for PSL at 10 mg daily to be continued. Therefore, we suggest that extending the duration of PSL treatment at 10 mg per day may decrease the rate of recurrence. The recurrence rate of SAT was about 20% in our study. SAT is recognized to be self-limited disease, but the recurrence of SAT would be troublesome. The modified protocol should be further investigated to decrease the recurrence rate of SAT.

In conclusion, recurrence rate of SAT with treated PSL is about 20%. It is not possible to determine before treatment which patients will recur. A modified treatment protocol is needed to reduce the recurrence rate of SAT.

References